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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/537,088	03/29/2000	Anil Kumar Dwivedi	82239	7351

7590 02/03/2003

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EXAMINER	
RUSSEL, JEFFREY E	

ART UNIT	PAPER NUMBER
1654	15

DATE MAILED: 02/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/537,088	DWIVEDI ET AL.	
	Examiner	Art Unit	
	Jeffrey E. Russel	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11,14 and 15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11,14 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Claims 1, 2, 5-9, 11, and 14 are rejected under 35 U.S.C. 103(a) as being obvious over the Nath et al article in view of Chiesi et al. The Nath et al article teaches the highly active opioid peptide L-Tyr-D-Ala-Gly-NMe-Phe-Gly-NHC_3H_7. The opioid peptide can be administered orally or i.p. See, e.g., the Abstract and page 269, column 1. The Nath et al article does not teach the opioid peptide in combination with a cyclodextrin derivative. Chiesi et al teach forming an inclusion complex of a basic drug and a cyclodextrin such as hydroxypropyl-β -cyclodextrin and dimethyl-β- cyclodextrin. The inclusion complex results in improved storage stability and enhanced water solubility and bioavailability for the drug. The drug is to be administered orally or parenterally. See, e.g., column 3, lines 15-21; column 8, lines 54-56; and claim 8. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to combine the opioid peptide of the Nath et al article with the cyclodextrins of Chiesi et al in order to form inclusion complexes for pharmaceutical administration because the opioid peptide of the Nath et al article is a basic drug as required by Chiesi et al and because combining the opioid peptide of the Nath et al article with the cyclodextrins of Chiesi et al would have been expected to increase the solubility and bioavailability of the opioid peptides, a result which is desirable for pharmaceutical agents. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal ratios of opioid peptide and cyclodextrin derivative in the above-outlined compositions because component proportion is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical art.

3. Claims 1-3, 7-9, and 11 are rejected under 35 U.S.C. 103(a) as being obvious over the European Patent Application '653 in view of the Nath et al article. The European Patent Application '653 teaches combining drugs, including peptide drugs such as enkephalins, with cyclodextrins, especially β-cyclodextrin. The combination permits the drugs to be administered nasally, thereby avoiding the problems of poor absorption after oral administration and avoiding undesirable metabolism of the drugs. See, e.g., column 1, lines 8-24; column 4, lines 4-11; and column 5, lines 31-36. The European Patent Application '653 does not teach administration of Applicants' particular opioid peptide. The Nath et al article teaches the highly active opioid peptide L-Tyr-D-Ala-Gly-NMe-Phe-Gly-NHC_3H_7. The opioid peptide can be administered orally or i.p. See, e.g., the Abstract and page 269, column 1. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to administer the opioid peptide of the Nath et al article in the pharmaceutical formulations of the European Patent Application '653 because the opioid peptide of the Nath et al article is a specific known example of the peptide and enkephalin drugs which are contemplated by the European Patent Application '653 and because administering the opioid peptide of Nath et al nasally in the pharmaceutical formulations of the European Patent Application '653 would avoid problems of poor absorption after oral administration and of undesirable metabolism as taught by the European Patent Application '653. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal ratios of opioid peptide and β-cyclodextrin in the above-outlined compositions because component proportion is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical art.

4. Claims 1, 2, 4, 7-9, 11, and 14 are rejected under 35 U.S.C. 103(a) as being obvious over Hora et al in view of the Nath et al article. Hora et al teach combining polypeptide drugs with cyclodextrins, β-cyclodextrin, including hydroxyethyl-β-cyclodextrin. The combination improves the solubility and the stability of polypeptide drugs, and permits oral administration as well. See, e.g., the Abstract; column 10, lines 31-45, column 11, lines 59-64; column 16, lines 30-32 and 43; column 18, lines 45-49; and column 26, line 66 - column 27, line 4. Hora et al do not teach administration of Applicants' particular opioid peptide. The Nath et al article teaches the highly active opioid peptide L-Tyr-D-Ala-Gly-NMe-Phe-Gly-NHC_3H_7. The opioid peptide can be administered orally or i.p. See, e.g., the Abstract and page 269, column 1. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to administer the opioid peptide of the Nath et al article in the pharmaceutical formulations of Hora et al because the opioid peptide of the Nath et al article is a specific known example of the polypeptide drugs which are contemplated by Hora et al and because administering the opioid peptide of Nath et al in the pharmaceutical formulations of Hora et al would improve the solubility and the stability of the opioid peptide as taught by Hora et al. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal ratios of opioid peptide and β-cyclodextrin in the above-outlined compositions because component proportion is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical art.

5. Claims 1, 7-9, 11, and 15 are rejected under 35 U.S.C. 103(a) as being obvious over the French Patent '268 in view of the Nath et al article. The French Patent '268 teaches combining drugs, including analgesics and peptide hormones, with β-cyclodextrin. The combination

permits the drugs to be administered transcutaneously. See the attached abstract. The French patent '268 does not teach administration of Applicants' particular opioid peptide. The Nath et al article teaches the highly active opioid peptide L-Tyr-D-Ala-Gly-NMe-Phe-Gly-NHC_3H_7. The opioid peptide can be administered orally or i.p. See, e.g., the Abstract and page 269, column 1. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to administer the opioid peptide of the Nath et al article in the pharmaceutical formulations of the French Patent '268 because the opioid peptide of the Nath et al article is a specific known example of the analgesic drugs which are contemplated by the French Patent '268, because the French Patent '268 would have been expected to be useful in transcutaneously administering polypeptides such as the opioid peptide of the Nath et al article because of the French Patent '268's disclosed ability to administer polypeptide hormones, and because administering the opioid peptide of Nath et al transcutaneously in the pharmaceutical formulations of the French Patent '268 would avoid problems of poor absorption after oral administration or of intrusive i.p. administration methods. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal ratios of opioid peptide and β-cyclodextrin in the above-outlined compositions because component proportion is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical art.

6. Applicant's arguments filed December 24, 2002 have been fully considered but they are not persuasive.

The examiner maintains his position for the reasons of record in this application, and especially for the reasons set forth in section 8 of the Office action mailed June 25, 2002.

With respect to the rejection based upon the combination of the Nath et al article and Chiesi et al, Applicants argue that the "consisting essentially of" terminology in the instant clams excludes the acid which is required by Chiesi et al. The examiner reiterates that the issue is not whether the additional ingredient is critical to the prior art composition, but rather is whether the additional ingredient materially affects the basic and novel characteristics of Applicants' claimed compositions. Applicants' specification, e.g., at page 5, lines 2-3, recites that increased water solubility is a goal of Applicants. An ingredient which is disclosed by the prior art (i.e. the acid of Chiesi et al) as helping to achieve this goal of Applicants does not materially affect the basic and novel characteristics of Applicants' claimed compositions. Applicants argue that the "consisting essentially of" terminology excludes even those additional ingredients which positively affect the characteristics of Applicants' invention (see page 9, lines 7-10, and page 10, 11-12, of the response). However, the examiner could not find support for this argument in any of the cited cases, and Applicants are requested more specifically to point the support for this position so that the examiner can more fully respond to the argument. In any event, the argument that the "consisting essentially of" excludes any additional components which have "some effect on a basic characteristic of the invention" can not be accepted, because any ingredient will inherently have "some" effect on a basic characteristic of an invention, and Applicants' argument would in effect reduce "consisting essentially of" language to "consisting of" language. The arguments that there is no motivation to modify the Nath et al article because the peptide is already soluble in water and stable, and that there is no reasonable expectation of success in forming orally available inclusion complexes, are addressed at page 6, last paragraph, through page 7 of the Office action mailed June 25, 2002.

The rejection based upon the combination of the European Patent Application '653 and the Nath et al article set forth in the previous Office action is maintained. For reasons analogous to those set forth above with respect to Chiesi et al's enhancers, the absorption enhancers of the European Patent Application '653 are not excluded by Applicants' "consisting essentially of" terminology. The examiner disagrees with Applicants' summary of the claimed invention set forth at page 16, lines 5-7, of the response. Method claim 11 only recites administering the compositions, and does not require oral administration. Method claim 15, also dependent upon independent composition claim 1, specifically recites topical administration. The prior art need not suggest oral administration in order to establish prima facie obviousness of Applicants' compositions claims, or to establish prima facie obviousness of those method claims which do not specify oral administration. Applicants argue that the compositions of the European Patent Application '653 are not orally efficacious. This argument is contradicted by the disclosure of the European Patent Application '653 at column 7, lines 16-17. In any event, a statement in the background of the invention concerning the oral administration of a drug per se (the examiner assumes that Applicants are referring to column 1, lines 11-15, of the European Patent Application '653) is not the equivalent of a statement that the inventive compositions of the European Patent Application '653 themselves are not orally efficacious. Applicants argue that the European Patent Application '653 does not disclose either the claimed specific opioid peptide itself or any other modification of enkephalin molecules. The examiner agrees; however, as the rejection is not an anticipation rejection but rather is an obviousness rejection based upon a combination of references, the argument is not convincing. As to the lack of any "practical demonstrations" regarding the disclosed drugs in the European Patent Application '653, such

demonstrations, examples, etc. are not a requirement to apply a reference under 35 U.S.C. 102 and/or 103. See MPEP 2121 and 2121.01 as to the issue of enablement and references applied under 35 U.S.C. 103.

The rejection based upon the combination of Hora et al and the Nath et al article set forth in the previous Office action is maintained. Applicants argue that inclusion complexes are not formed in the compositions of Hora. The examiner does not agree. A specific example of Hora et al indicates that complexes are formed between its polypeptides and its cyclodextrin derivatives (see column 25, lines 3-6). Further, the examiner does not agree that any special conditions are required to form inclusion complexes involving cyclodextrins. Hora et al's specification at column 7, lines 52-61, and at column 25, lines 3-6, indicates that mere mixing is sufficient to form inclusion complexes. Concerning Applicants' argument with respect to peptide:cyclodextrin ratio, see page 8, first paragraph, of the previous Office action. Concerning Applicants' argument at page 24, first full paragraph, of the response, the word "most" does not occur anywhere in the cited section of Hora et al. Further, this section of Hora et al's disclosure can not be taken out of context to contradict the purpose of Hora et al's invention (see, e.g., the Title, the Abstract, and column 19, lines 51-58; see also the word "However" at claim 19, line 51, which distinguishes Hora et al's invention from the preceding discussion of untried agents). The statement in Hora et al relied upon by Applicants applies to untried agents, not to those tried and claimed by Hora et al.

The rejection based upon the combination of the French Patent '268 and the Nath et al article set forth in the previous Office action is maintained. As noted above, instant claim 11 does not require oral administration, and instant claim 15 positively recites topical

administration. Accordingly, Applicants' arguments which are based upon the distinction between oral administration and transcutaneous administration are not convincing. As has been argued by the examiner, the rationale to combine references under 35 U.S.C. 103 need not be the same as Applicants' rationale. Accordingly, even if the motivation is based upon the desirability of forming transcutaneously administrable compositions, as long as the same composition as is claimed by Applicants is suggested, prima facie obviousness is established. The examiner does not agree that the French Patent '268's disclosure of transcutaneous administration shows that the reference's compositions are not orally efficacious. This disclosure of the French Patent '268 only means that oral administration of the compositions has not been considered. There is no evidence of record that the compositions of the French Patent '268 are not orally efficacious. Again, the implication of the French Patent '268 that individual drugs per se are difficult to administer orally or are ineffective when administered orally does not mean that compositions comprising the drug are difficult to administer orally. Compositions comprising drugs have different pharmaceutical properties than the drugs per se. In re Fine, cited by Applicants, does not contradict MPEP 2144, under "Rationale Different From Applicant's Is Permissible".

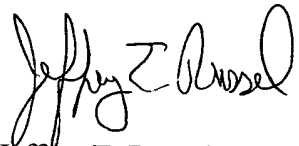
7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (703) 308-3975. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Brenda Brumback can be reached at (703) 306-3220. The fax number for Art Unit 1654 for formal communications is (703) 305-3014; for informal communications such as proposed amendments, the fax number (703) 746-5175 can be used. The telephone number for the Technology Center 1 receptionist is (703) 308-0196.



Jeffrey E. Russel

Primary Patent Examiner

Art Unit 1654

JRussel

January 27, 2003